AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Withdrawn) Process for specifically modulating the properties of an intracellular target molecule T, and/or of a cellular component C which interacts directly or indirectly in a cell with T, said process comprising :

introducing into a cell a chimeric molecule, a so-called « targeted effector », comprising:

- a recognition moiety R, comprising a peptide V having a length of five to sixty amino acids, *preferably ten to forty amino acids*, conformationally constrained by covalent linking to a platform, said recognition moiety R having the capacity to specifically interact, within the cell, with a site on an intracellular target molecule T, the interaction with T occurring with an affinity A_1, and
- an effector moiety, E, covalently linked to said recognition moiety R, E being a molecule, or a portion thereof, which has an initial capacity to exert an effect on at least one molecule M, and which when it is covalently linked to R, acquires the capacity to exert the effect on the intracellular target molecule T,

wherein the targeted effector interacts with T with a second affinity A_2, the affinity A_1 or the affinity A_2 corresponding to a K_d of less than 1×10^{-8} M, and the properties of T and / or of C are specifically modulated by the effector moiety E.

2. (Withdrawn) Process according to claim 1 wherein the peptide V has a length of six to forty amino acids,

3. (Withdrawn) Process according to claim 1 wherein the peptide V comprises a random peptide.

4. (Withdrawn) Process according to any one of claims 1 to 3 wherein the platform comprises or consists of a protein.

5. (Withdrawn) Process according to any one of claims 1 to 4 wherein the platform is heterologous with respect to the peptide V.

6. (Withdrawn) Process according to claim 5 wherein the peptide V is embedded in the platform.

7. (Withdrawn) Process according to claim 5 wherein said platform is thioredoxin (TRX) or a TRX-like protein.

8. (Withdrawn) Process according to Claim 1 wherein the binding affinity A_1 corresponds to a K_d comprised between 1×10^{-9} M and 1×10^{-12} M.

9. (Withdrawn) Process according to claim 1 wherein R is a mutant of a parent recognition moiety R_a, said parent recognition moiety R_a having the capacity to specifically interact with a site on said intracellular target molecule T, the interaction between R_a and T occurring with an affinity A_3, wherein the K_d corresponding to A_3 is greater than the K_d corresponding to A_1.

10. (Withdrawn) Process according to claim 1 wherein E has the initial capacity to exert an effect *in cis* and / or *in trans* on M, and, when it is covalently bound to R, acquires the capacity to exert the effect *in trans* on T.

11. (Withdrawn) Process according to claim 1 wherein the effector moiety E comprises an enzyme, a co-factor, an addressing signal, a transcription regulatory protein, a tracer

protein, a molecule having therapeutic or diagnostic properties, a second recognition moiety, a second targeted effector, a radionuclide, a chemical modifier.

12. (Withdrawn) Process according to claim 1 wherein the effector moiety E comprises a second recognition moiety R_2 having the capacity to specifically interact, within a cell, with a site on an intracellular target molecule T_2, T_2 being a target molecule which is distinct from T

13. (Withdrawn) Process according to claim 1 wherein the effector moiety E is not a transcription activator.

14. (Withdrawn) Process according to claim 6 wherein the effector moiety E is covalently bound to the amino or carboxy terminal of the recognition moiety R.

15. (Withdrawn) Process according to claim 1 wherein the identity of T and / or C is predetermined.

16. (Withdrawn) Process according to claim 1 or 15, wherein the target molecule T or the cellular component C comprises a protein, a nucleic acid, a carbohydrate, a phosphorylated molecule, a lipid, or a combination of any of the foregoing.

17. (Withdrawn) Process according to claim 1 wherein the target protein T and / or the cellular component C is/are endogenous to the cell.

18. (Withdrawn) Process according to claim 1 wherein the target protein T is a protein comprising at least two functionally distinct protein domains, T_a and T_b, and wherein the recognition moiety R specifically binds to domain T_a and the effector moiety E

exerts the effect on domain T_b.

19. (Withdrawn) Process according to claim 1 wherein R has the capacity to specifically interact, within the cell, with a site on a predetermined range of target molecules, including T, and the effector moiety E, when it is covalently bound to R, acquires the capacity to exert the effect *in trans* in the cell on the said predetermined range of intracellular target molecules.

20. (Withdrawn) Process according to claim 1 wherein R interacts with a site occurring within the cell exclusively on T.

21. (Withdrawn) Process according to claim 1 wherein the recognition moiety R, in the absence of the effector moiety E, is neutral with respect to the function of the target protein T.

22. (Withdrawn) Process according to claim 1 wherein the property of T and / or C which is modulated by E is a chemical, biochemical, physical and / or functional property.

23. (Withdrawn) Process according to claim 22 wherein the modulation of the chemical, biochemical, physical, or functional properties of the target protein T or the cellular component C gives rise to a phenotypical change in the cell or organism, said phenotypical change being optionally selectable or detectable.

24. (Withdrawn) Process according to claim 22 wherein the change in the chemical properties of T and / or C comprises the formation or breakage of covalent or non-covalent bonds.

25. (Withdrawn) Process according to claim 22 wherein the change in the physical properties of T and / or C comprises a change in conformation, or in sub-cellular localisation.

26. (Withdrawn) Process according to claim 22 wherein the change in the functional properties of T and / or C comprises the enhancement or reduction in the efficiency of one or more of the functions of T and / or C, or the abolition of a function, or the creation of a new function.

27. (Withdrawn) Process according to claim 22 wherein the modulation gives rise to one or more of the following effects :

- homo- or heterodimerisation of T or C ;
- inhibition of homo- or heterodimerisation of T or C ;
- destruction of T or C ;
- stabilisation of T or C ;
- labeling of T or C ;
- ability of T or C to interact with a new partner ;
- localisation of T or C to a subcellular compartment to which T or C are not otherwise transported in the cell ;
- localisation of T or C to a subcellular compartment to which T or C are otherwise transported to a lesser degree in the cell ;
- exposure of T or C at the cell membrane ;
- internalisation of T or C ;
- provoking the association of T or C with natural intracellular partners ;
- prevention of the association of T or C with natural intracellular partners ;
- cleavage of T or C ;
- secretion of T or C ;

- modification of cell cycle dynamics.

28. (Withdrawn) Process according to claim 1 wherein the cell is a eukaryotic cell.

29. (Withdrawn) Process according to claim 1 wherein the cell is a prokaryotic cell.

30. (Withdrawn) Process according to claim 1 wherein the targeted effector is introduced into the cell by expression of a DNA sequence encoding said targeted effector as a fusion protein.

31. (Withdrawn) Process according to claim 1 wherein the targeted effector is introduced into the cell in purified form using a cell permeable agent such as a protein transduction domain.

32. (Withdrawn) Process according to claim 1 wherein, in a given set of conditions in the cell, the effector moiety E has the capacity to exert an effect on T when it is covalently bound to the recognition moiety, but cannot exert the said effect on T or C when it is not covalently bound to the recognition moiety, in said conditions.

33. (Withdrawn) Process according to claim 32 wherein the inability of the effector moiety E to exert the effect on T or C in the cell when it is not covalently bound to the recognition moiety is due to the inherent specificity of E or T.

34. (Withdrawn) Process according to claim 33 wherein the effector moiety E is an enzyme whose inherent specificity prevents the target protein T from acting as substrate for E when E is not covalently linked to the recognition moiety.

35. (Withdrawn) Process according to claim 32 wherein the inability of the effector moiety E to exert said effect on T or C in said cell when it is not covalently bound to the recognition moiety is due to lack of co-expression of E and T and/or C.

36. (Withdrawn) Process according to claim 32 wherein T and / or E exhibit a temporal or spatial specificity which prevents the effector moiety E and the target molecule T from associating with each other when E is not covalently linked to the recognition moiety R.

37. (Withdrawn) Process according to claim 1 wherein the effector moiety E initially has the capacity to direct an intracellular molecule M *in cis* to a predetermined sub-cellular compartment, and acquires the capacity to direct the target molecule T *in trans* to the said sub-cellular compartment when E is covalently linked to R.

38. (Withdrawn) Process for the production of a targeted effector having the capacity to specifically modulate the properties of an intracellular target molecule T, and / or a cellular component C which interacts directly or indirectly in a cell with T, said process comprising the steps :

a) production of a random pool of peptides, so-called recognition moieties R,

b) screening of the random pool produced in (a) against T in a cell, in conditions suitable to allow identification of recognition moieties R capable of interacting with T,

c) optionally contacting the moieties selected in (b) with proteins other than T to determine the specificity range of each of said moieties, and to identify moieties having a desired specificity range,

d) covalent linkage of the recognition moieties R to an effector moiety E,, E being a molecule which initially has the capacity to exert a predetermined effect on at

least one intracellular component M,

step (d) being carried out either prior to step (b), or after step (e),

e) verification of the affinity A_1 with which the recognition moiety R interacts with T, or of the affinity A_2 with which the targeted effector, interacts with T,

f) if both of A_1 and A_2 correspond to K_d values greater than 1×10^{-8} M, alteration of the binding region of the recognitio moiety to adjust the binding affinity of the interaction between T and the selected moiety so that the K_d becomes less than 1×10^{-8} M.

39. (Withdrawn) Process according to Claim 38 wherein step (b) comprises the screening of the pool of random peptides in a cell for a detectable or selectable phenotypic change occurring via an interaction with an unknown endogenous target T, or via a modification of T by E when step (d) is carried out prior to step (b).

40. (Withdrawn) Process according to Claim 39 further comprising the step of determining the identity of T by screening selected recognition moieties against molecules known to have the capacity to give rise to said phenotypic change.

41. (Withdrawn) Process according to Claim 39 further comprising the step of determining the identity of T by performing a two-hybrid screen using R or the targeted effector R-E as bait.

42. (Withdrawn) Process according to Claim 38 wherein step (b) comprises the screening of the pool of random peptides in a cell against a known target molecule T, interaction with T giving rise to a detectable or selectable change.

43. (Withdrawn) Process according to Claim 38 wherein step (b) comprises detection of reporter gene transcription in a two-hybrid interaction trap system, candidate target proteins being co-expressed in the cell with the recognition moieties.

44. (Withdrawn) Process for conferring on an effector moiety E the ability to specifically modulate the properies of an intracellular protein T, or an intracellular component C which interacts directly or indirectly with T,

said process comprising the steps of

i) covalently linking the effector moiety E to a recognition moiety R,

wherein R comprises a molecule having the capacity to specifically interact, within a cell, with a site on an intracellular target molecule T, the interaction with T occurring with an affinity A_1 which corresponds to a K_d value of less than 1 x 10^{-8} M, and

E being a molecule which has an initial capacity to exert an effect on at least one molecule M, and which when it is covalently linked to R, acquires the capacity to exert the effect on the intracellular target molecule T,

ii) optionally optimising the affinity of the interaction between T and R by altering the chemical composition of the binding region of R to provide an affinity in the desired range.

45. (Withdrawn) Chimeric molecule, so-called « targeted effector », said targeted effector comprising

- a proteinaceous recognition moiety R, comprising a peptide V having a length of five to sixty amino acids, preferably ten to forty amino acids, conformationally constrained by covalent linking to a platform, said recognition moiety R having the capacity to specifically interact, within a cell, with a site on an intracellular target molecule T, the interaction with T occurring with an affinity A_1, and

- an effector moiety, E, covalently linked to R, E being a molecule which has an initial capacity to exert an effect on at least one molecule M, and which when it is covalently linked to R, acquires the capacity to exert the effect on the intracellular target molecule T,

wherein the targeted effector interacts with T with an affinity A_2, the affinity A_1 or the affinity A_2 corresponding to a K_d value of less than 1×10^{-8} M.

46. (Withdrawn) Chimeric molecule according to claim 45 wherein the peptide V comprises a random peptide.

47. (Withdrawn) Chimeric molecule according to claim 45 or 46 wherein the platform comprises or consists of a protein.

48. (Withdrawn) Chimeric molecule according to claim 47 wherein the platform is heterologous with respect to the peptide V.

49. (Withdrawn) Chimeric molecule according to claim 48 wherein said platform is thioredoxin (TRX) or a TRX-like protein.

50. (Withdrawn) Chimeric molecule according to claim 45 wherein the binding affinity A_1 corresponds to a K_d value of less than 1×10^{-9} M.

51. (Withdrawn) Chimeric molecule according to any one of claims 45 to 50 wherein the effector moiety E comprises an enzyme, a co-factor, an addressing signal, a transcription regulatory protein, a tracer protein, a target for intracellular enzymes, a molecule having therapeutic or diagnostic properties, a second recognition moiety, a second targeted effector, a radionuclide, a chemical modifier.

52. (Withdrawn) Chimeric molecule according to claim 51 wherein the effector moiety E comprises a second recognition moiety R_2 having the capacity to specifically interact, within a cell, with a site on an intracellular target molecule T_2, T_2 being a target molecule which is different from T

53. (Withdrawn) Nucleic acid encoding a chimeric protein according to claim 45 operably linked to regulatory sequences for expression in a eukaryotic cell.

54. (Withdrawn) Vector capable of stably introducing a nucleic acid according to claim 53 into a prokaryotic or eukaryotic cell.

55. (Withdrawn) Cell containing a chimeric molecule according to claim 45, or a nucleic acid according to claim 53.

56. (Withdrawn) Cell according to claim 55 which is a eukaryotic cell.

57. (Withdrawn) Cell according to claim 55 which is a prokaryotic cell.

58. (Withdrawn) Pharmaceutical composition comprising a chimeric molecule according to claim 45, or a nucleic acid according to claim 53, in association with a pharmaceutically acceptable excipient.

59. (Withdrawn) Chimeric molecule according to claim 45 for use in therapy.

60. (Withdrawn) Nucleic acid according to claim 53 for use in therapy.

61. (Withdrawn) Use of a chimeric protein according to claim 45 or a nucleic acid according to claim 53 for the preparation of a medicament for the treatment of :

- microbial infections, including viral infections, and fungal infections ;
- immunological disorders ;
- neurological disorders ;
- metabolic disorders ;
- psychiatric disorders ;
- myopathies ;
- genetic disorders ;
- cancer ;
- cardiovascular disorders ;
- dental disorders;
- aesthetic disorders.

62. (Withdrawn) Use of a chimeric protein according to Claims 45 to 52, or a nucleic acid according to claim 53 for specifically modulating the properties of an intracellular target molecule T, and / or a cellular component C which interacts directly or indirectly in a cell with T.

63. (Previously Presented) An intracellular recognition molecule R, comprising a proteinaceous recognition domain, conformationally constrained by covalent bonding to a platform, said recognition molecule R specifically interacting, within a cell, with a site on a predetermined intracellular target molecule T, the interaction with T occurring with an affinity corresponding to a K_d value of less than or equal to 5×10^{-9} M, wherein said intracellular recognition molecule R is a peptide aptamer, wherein said platform is thioredoxin (TRX) or a TRX-like protein, and wherein the proteinaceous recognition domain consists of a peptide

having a length of five to sixty amino acids.

64. (Previously Presented) The intracellular recognition molecule R according to claim 63 wherein the recognition domain consists of a peptide having a length of ten to forty amino acids.

65. (Previously Presented) The intracellular recognition molecule R according to claim 64 wherein the peptide recognition domain comprises a random peptide.

66. (Cancelled)

67. (Previously Presented) The intracellular recognition molecule R according to claim 64, wherein the platform is heterologous with respect to the recognition domain.

68. (Cancelled)

69. (Previously Presented) The intracellular recognition molecule according to claim 63, wherein the affinity of the interaction with T corresponds to a K_d value comprised between 1×10^{-9} M and 1×10^{-14} M.

70. (Currently Amended) The intracellular recognition molecule according to claim 63, wherein the intracellular target molecule T with which R specifically interacts is chosen from a cyclin-dependent kinase[[,]] and a pro-apoptotic protein.

71. (Previously Presented) The intracellular recognition molecule according to claim 70 wherein the intracellular target molecule T is Cdk2.

72. (Previously Presented) The intracellular recognition molecule according to claim 71 wherein the peptide recognition domain comprises a mutant of the amino acid sequence QVWSLWALGWRWLRRYGWNM (SEQ ID NO:1), said mutant having from one to three amino acid changes with respect to said sequence.

73. (Previously Presented) The intracellular recognition molecule according to claim 72 wherein the peptide recognition domain comprises the amino acid sequence QVWSSWALGWRWLRRYGWGM (SEQ ID NO:2).

74. (Previously Presented) The intracellular recognition molecule according to claim 70 wherein the intracellular target molecule T is Bax.

75. (Previously Presented) The intracellular recognition molecule according to claim 74 wherein the peptide recognition domain comprises a mutant of the amino acid sequence P R G A P M W M R W V C Q M L E T M F L (SEQ ID NO:3), said mutant having from one to three amino acid changes with respect to said sequence.

76. (Previously Presented) The intracellular recognition molecule according to claim 75 wherein the peptide recognition domain comprises the amino acid sequence P R G A P M W L R C V C Q M L E T K F L (SEQ ID NO:4).

77. (Currently Amended) An oligomeric intracellular recognition molecule, comprising from two to four intracellular recognition molecules R, each ~~of which~~ being an intracellular recognition molecule according to claim 63, said recognition molecules being covalently linked to each other, either directly or via a linker.

78. (Previously Presented) The oligomeric intracellular recognition molecule according to claim 77 comprising two intracellular recognition molecules R.

79-82. (Cancelled)

83. (Withdrawn) Process for the identification of dimeric recognition moieties having the capacity to force an interaction between two target molecule T1 and T2, and / or a cellular component C which interacts directly or indirectly in a cell with T1 or T2, said process comprising the steps :

a) production of a random pool of peptides, so-called recognition moieties R,

b) screening of the random pool produced in (a) against T1 and T2 in a cell, in conditions suitable to allow identification of recognition moieties R capable of interacting with T1 or T2,

c) optionally contacting the moieties selected in (b) with proteins other than T1 and T2 to determine the specificity range of each of said moieties, and to identify moieties having a desired specificity range,

d) covalent linkage of two thus-identified recognition moieties R1 and R2 to each other to provide a dimeric recognition moiety,

e) screening of the dimeric recognition moiety to identify moieties capable of interacting simultaneously with T1 and T2.

84. (Previously Presented) The intracellular recognition molecule R according to claim 63 wherein the recognition domain consists of 20 amino acids.

85. (New) An intracellular recognition molecule R, comprising a proteinaceous recognition domain, conformationally constrained by covalent bonding to a

platform, said recognition molecule R specifically interacting, within a cell, with a site on a predetermined intracellular target molecule T, the interaction with T occurring with an affinity corresponding to a K_d comprised between 5×10^{-9} M and 1×10^{-14} M, wherein said intracellular recognition molecule R is a peptide aptamer, wherein said platform is thioredoxin (TRX), a human thioredoxin, or a glutaredoxin and wherein the proteinaceous recognition domain consists of a peptide having a length of five to sixty amino acids.

86. (New) The intracellular recognition molecule according to claim 85, wherein the intracellular target molecule T with which R specifically interacts is chosen from a cyclin-dependent kinase and a pro-apoptotic protein.

87. (New) The intracellular recognition molecule according to claim 86, wherein the intracellular target molecule T is Cdk2.

88. (New) The intracellular recognition molecule according to claim 85, wherein the peptide recognition domain comprises a mutant of the amino acid sequence QVWSLWALGWRWLRRYGWNM (SEQ ID NO:1), said mutant having from one to three amino acid changes with respect to said sequence.

89. (New) The intracellular recognition molecule according to claim 85, wherein the peptide recognition domain comprises the amino acid sequence QVWSSWALGWRWLRRYGWGM (SEQ ID NO:2).

90. (New) The intracellular recognition molecule according to claim 85, wherein the intracellular target molecule T is Bax.

91. (New) The intracellular recognition molecule according to claim 85, wherein the peptide recognition domain comprises a mutant of the amino acid sequence P R G A P M W M R W V C Q M L E T M F L (SEQ ID NO:3), said mutant having from one to three amino acid changes with respect to said sequence.

92. (New) The intracellular recognition molecule according to claim 85, wherein the peptide recognition domain comprises the amino acid sequence P R G A P M W L R C V C Q M L E T K F L (SEQ ID NO:4).